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SARS-CoV-2 as a cause of fatal intestinal perforation

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Abstract

Gastrointestinal (GI) perforation in association with COVID-19 is uncommonly reported in the literature. In this study, our goal was to elucidate the possible pathologic role of SARS-CoV-2 on the GI tract in a patient suffering from intestinal perforation. A literature review using PubMed identified 40 additional cases of COVID-19-related GI perforation. Including our case, a total of 41 cases has been described in the literature, 18 of which were fatal. Including our case, in only three cases SARS-CoV-2 RNA was detected in intestinal surgical specimens. The detection of Sars-Cov-2 viral RNA in GI tissue samples has not been adequately standardized, and consistent results are lacking. Regular testing for SARS-CoV-2 in biopsy and surgical specimens would be necessary to establish its true, direct pathological role in the GI manifestations associated with COVID-19, also in those patients with severe illness or on treatments like glucocorticoids and tocilizumab.

Introduction

Gastrointestinal (GI) perforation in association with COVID-19 and the detection of Sars-CoV-2 RNA on intestinal specimens is uncommonly reported in the literature. We describe a case of spontaneous small bowel perforation in a patient suffering from COVID-19, along with the detection of Sars-CoV-2 viral RNA in the surgical specimens. The association between the

detection of virus and its concentration in intestinal samples with the severity of the GI disease has been rarely reported.[1-4]

Case Report

A 74-year-old male patient with Chronic Lymphocytic Leukemia (CLL) and severe chronic cerebrovascular disease was evaluated in the Emergency Department of our hospital on July 23, 2022, for widespread and worsening abdominal pain, associated with hyperpyrexia and melena. CLL originates from B-cells lymphocytes and no immediate treatment was started, as it was an initial and asymptomatic form, monitoring its evolution with periodic checks.

The patient had previously received three doses of the COVID-19 vaccine, but this was not further specified. Testing for SARS-CoV-2 in nasopharyngeal swab on Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) assay was positive.

Laboratory blood test at admission are reported on table 1.

A Computerized Tomography (CT) scan of the thorax revealed subpleural reticular opacities at the right basal pyramid, suggestive for mild-to-moderate pneumonia.

A CT scan of the abdomen documented an ischemic jejunal perforation, with fluid distention of the mesenteric small bowel loops, thickening of the skin folds, the presence of some air-fluid levels, and an air-filled collection with heterogeneous local adipose tissue on the right flank. There was also evidence of lymphadenopathies, and the presence of hyperdense material in the lumen of the descending colon and sigmoid colon, in the absence of active bleeding.

The patient underwent emergency repair of the jejunal perforation, with resection of approximately 80 cm of jejunum and creation of a jejunal-intestinal anastomosis.

Medical treatment included both the monoclonal antibody sotrovimab (Xevudy) and remdesivir (Veklury), 200 mg on day 1, then 100 mg/day from day 2 to day 5, thus achieving negative SARS-CoV-2 viremia two days after the end of antiviral therapy. For concurrent peritoneal involvement, piperacillin-tazobactam and metronidazole were administered.

The macroscopic pathological examination revealed a 35 cm intestinal resection, covered by a fibrinous coating, and a fissure of approximately 0.5 cm was found (Figure 1).

Histological examination of the jejunal sections revealed the presence of widespread acute necrotic-purulent inflammation of the perivisceral serosa (Figure 2 and 3).

The search for some SARS-COV-2 viral genes, Omicron 5, also known as BA.5, in the intestinal epithelium resulted positive on a RT-PCR assay. Specifically, in two outermost areas, the search for the ORF8 gene was positive, with a low titer of 37 copies/microg RNA, while in two other

innermost areas, near blood vessels, the search for the RdRp gene was positive, with a low titer of 38 copies/microg RNA.

The patient's clinical condition progressively worsened, resulting in multiorgan failure, which led to death after a few days.

Discussion

GI manifestations in SARS-CoV2 infection was found to be related to various biochemical and molecular tools[1-2].

The disease impact on the architecture and cellularity of ileal Peyer's Patches (PP) resulting from a depletion of Germinal Centers (GC), a disruption of B cell/T cell zonation, a decreased potential B and T cell interaction and a lower nuclear density.[3]

GI perforation is an uncommon but potentially serious complication of COVID-19, and may occur even several weeks after COVID-19 diagnosis.

Cases of GI perforations in COVID-19 patients reported in the current literature are summarized (Table 2).[4-15]

Analyzing the case descriptions presented in the different published articles, it emerges that the detection of SARS-CoV-2 RNA in GI biopsy specimens and surgical samples has been rarely reported. A literature review using PubMed database identified 40 cases of COVID-19-related GI perforation,[4-15] 18 of which had an unfavorable outcome. The colon and the rectum were the most frequently affected intestinal tracts.

The detection of viral RNA or the isolation of the virus in stool samples have been reported in previous studies which enrolled only a limited number of cases, while the first and largest study on the detection of viral RNA in GI tissue samples has been adequately investigated recently.

Considering the intestinal tract could represent an additional tropism site for SARS-CoV-2, based on several observations suggesting that enteric infections can occur in COVID-19 patients, Cuicchi *et al.*[4] conducted a study on a large number of patients, with the primary objective of detecting SARS-CoV-2 RNA and evaluating histological features in a large number of biopsy or surgical tissue samples. Viral RNA was not detectable in any of the 53 rectal biopsies performed, while viral RNA was detected in two surgical specimens of the six examined, both of which were from patients with active neoplastic disease who underwent emergency intestinal resection.[4]

In these cases, viral RNA, with a low titer (< 25 copies/microg RNA in the first case and 29 copies/microg RNA in the second case) was detected in colonic tissue containing a neoplasm, with an intense infiltrate of macrophages, granulocytes and plasma cells of the muscle and adipose tissue.[4]

SARS-CoV-2 RNA was not detected in surgical specimens in any other cases reported in different articles. In only one case RT-PCR test for SARS-CoV-2 isolation performed in the gastric fluid resulted positive.[10]

Cases of GI tract perforation during COVID-19 are reported with increasing incidence, however, SARS-CoV-2 viral RNA has rarely been searched or detected in intestinal biopsy and surgical specimens.

Conclusions

The detection of SarsCov-2 viral RNA in GI tissue samples has not been adequately standardized, and consistent results are lacking. In order to confirm the role of SARS in causing clinically GI involvement, viral RNA detection on biopsy tissue or surgical specimens would be performed.

GI damage could result also from steroid therapy, immunomodulatory therapy, and any associated antibiotics, which can induce alterations in the intestinal microbiome and other tissue structural changes. Regular testing for SARS-CoV-2 in biopsy and surgical specimens would be necessary to establish its true, direct pathological role in the GI manifestations associated with COVID-19, including in patients with severe illness or on immunosuppressive therapies.

Based on the literature findings, we emphasize the importance that clinicians should maintain a high level of suspicion for the possible role of SARS-CoV-2 infection in cases of GI perforation in patients presenting to the emergency department with COVID-19 and signs of GI tract perforation, encouraging subsequent standardized and regular testing for viral RNA on surgical specimens.

Early diagnosis and immediate surgical intervention are crucial steps for managing this life-threatening complication, which has been described with increasing frequency.

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Table 1. Laboratory blood tests at admission.

Test	Results	Normal value
WBC	11.200/mL	4.000 – 11.0000
Haemoglobin	9.8 g/dL	12.0 – 17.5
Hematocrit	29%	36.0% - 46.0%
MCV	29 fl	80.0 – 100.0
Neutrophils	9,400/mL (84%)	2.000 – 8.000
Lymphocytes	900/mL (8%)	1.500 - 3.500
Mature T lymphocytes (cd3+) count	478/mL (60%)	690 – 2540 (55 - 84%)
Cytotoxic suppressor T lymphocytes (cd3+cd8+) count	180/mL (22%)	190 – 1140 (13 – 41%)
Inducing T lymphocytes (cd3+/cd4+) count	305/mL (37%)	410 – 1590 (31 – 60%)
Natural killer lymphocytes (CD16+56+) count	288/mL (37%)	90-590 (5-27%)
B lymphocytes (CD19+) count	12/mL (1%)	90 – 660 (6 – 25%)
Platelets	238.000/mL	150.000 – 450.000
Neutrophil/lymphocyte ratio	10	0.78 – 3.53
Platelet/lymphocyte ratio	264	90 - 210
Creatinin	1.57 mg/dL	0.55 – 1.18
Interleukin 6	1339 pg/mL	0.0 – 6.4
LDH	284 U/L	50 -248
D-dimer	1.66 ng/L	0,00 - 0,50
C-reactive protein	236 mg/L	0.0 – 5.0
Procalcitonin	7.654 ng/mL	0,00 - 0,09
Fibrinogen	628 mg/dL	150 - 450
Vitamin D	11 ng/mL	20 - 60
Ag SARS-CoV-2 N	Positive	
SARS-CoV-2 TrimericS IgG	140 BAU/mL	
Quantitative COVID-19 molecular diagnostics	2.392.154 copies/mL	

Table 2.Cases of GI perforations in COVID-19 patients reported in the current literature.

Reference, y, country	Age(y), Sex	Days of COVID-19 dx	Part of intestine	Management	Outcome	rRT-PCR SarsCov-2 detection in surgical specimens
De Nardi P et al., 2020,Italy	53,M	10	Ascending colon	Right colectomy + ileo-transverse anastomosis	Discharged	Not detected
Corrêa Neto IJ et al.,2020,Brazil	80,F	0	Sigmoid	Recto-sigmoidectomy + terminal colostomy	Died	NR
Almeida Vargas A et al.,2020,	76,M	NR	Ischemic colitis	Not operated	Died	N.R.
	68,M	NR	Cecum	Ileostomy	Died	N.R.
Rojo M et al.	56,M	15	Colon	Not operated	Died	
Nahas SC et al.,2020,Spain	54,F	0	Cecum	Right hemicolectomy	Died	
Persiano T et al.,2020,Brazil	92,M	11	Descending colon	Resection + terminal colostomy	Died	N.R. SARS-CoV-2 detected in the gastric fluid
Giuffrè M et al.,2020,Italy	87,F	0	Rectum	Not operated	Died 12 h after admission to the hospital	N.R.
Parhar G et al.,2020,USA	36,F	NR	Cecum	Right hemicolectomy + loop ileostomy	Died	N.R.
Verma D et al.,2020,India	60,F	11	Rectum	Transverse colostomy	Discharged	N.R.
	24,F	05	Caecum	Loop ileostomy	Discharged	N.R.
	21,M	0	Stomach	Graham patch	Discharged	N.R.
Bulte JP et al.,2021, Netherlands	65,M	28	Rectum	Diversion colostomy	Discharged	N.R.
	58,M	14	Cecum	Ileocecectomy + end ileostomy	Discharged	N.R.
	57,M	14	Transverse colon	Extended right hemicolectomy + end ileostomy	Discharged	N.R.

Estevez-Cerda SC et al.,2021,Mexico	34,M	07	Ascending colon	Right colectomy	Discharged	N.R.
	54,M	08	Ascending colon	Right colectomy	Discharged	N.R.
	69,M	16	Ascending colon	Right colectomy	Died	N.R.
	60,F	12	Sigmoid + Terminal ileum	Hartmann's resection + end to end anastomosis	Discharged	N.R.
Al Argan RJ et al., 2021,Saudi Arabia	70,M	44	Cecum	Not operated	Discharged	N.R.
	37,M	05	Ascending colon	Not operated	Discharged	N.R.
	74,M	04	Sigmoid	Hartman's resection + colostomy	Discharged	N.R.
Nakatsutsumi K et al., 2021, Japan	67,M	12	Transverse Colon	Resection & colostomy	Died	N.R.
Almeida A et al.,2021,Spain	79,M	NR	Sigmoid	Hartman's resection	Discharged	N.R.
Muñoz CA et al., 2021, Columbia	50,M	15	Hepatic Flexure	Primary closure & lavage	Discharged	N.R.
Morimoto Y et al., 2022, Japan	79,M	08	Sigmoid	Transverse colostomy	Discharged	N.R.
Chaugale SB et al., 2022, India	68,F	16	Sigmoid	Not operated	Discharged	N.R.
	57,F	19	Cecum	Percutaneous drainage	Discharged	N.R.
	72,M	18	Cecum	Percutaneous drainage	Discharged	N.R.
	25,M	22	Ascending colon	Percutaneous drainage	Discharged	N.R.
	56,M	24	Ascending colon	Repair of perforation + loop ileostomy	Died	N.R.
	71,M	17	Sigmoid	Not operated	Died	
Masanam MK et al., 2022, USA	82,F	14	Ascending colon	Right hemicolectomy + end ileostomy	Died	N.R.
	45,M	13	Right Colon	Ileocecectomy+ end ileostomy	Discharged	N.R.
	51,M	21	Cecum	Right Hemicolectomy	Died	N.R.

Cuicchi D et al., 2022,Italy	6 patients, age, range of age 56-93; sex not reported	A wide variety in time of diagnosis	Different digestive sites involved	Different types of surgical treatment	All 6 patients died	SARS-CoV-2 RNA was identified in 2 cases
Guiritan AT and Cataluña JG, 2023, Philippines	35,F	07	Cecum	Right hemicolectomy	Died	N.R.
John J et al.,2024, Qatar	38,M	29	Sigmoid colon	Hartmann's procedure	Discharged	N.R.
	33,M	07	Mid-transverse colon	A primary two-layer repair and later with a transverse loop colostomy	Discharged	N.R.
This report, 2025, Italy	74,M	00	Jejun	Jejunal-intestinal anastomosis	Died	SarsCov2-RNA detected

Abbreviations: y, year; dx, diagnosis; NR, not reported; rRT-PCR, real-time reverse-transcriptase–polymerase-chain-reaction analysis.

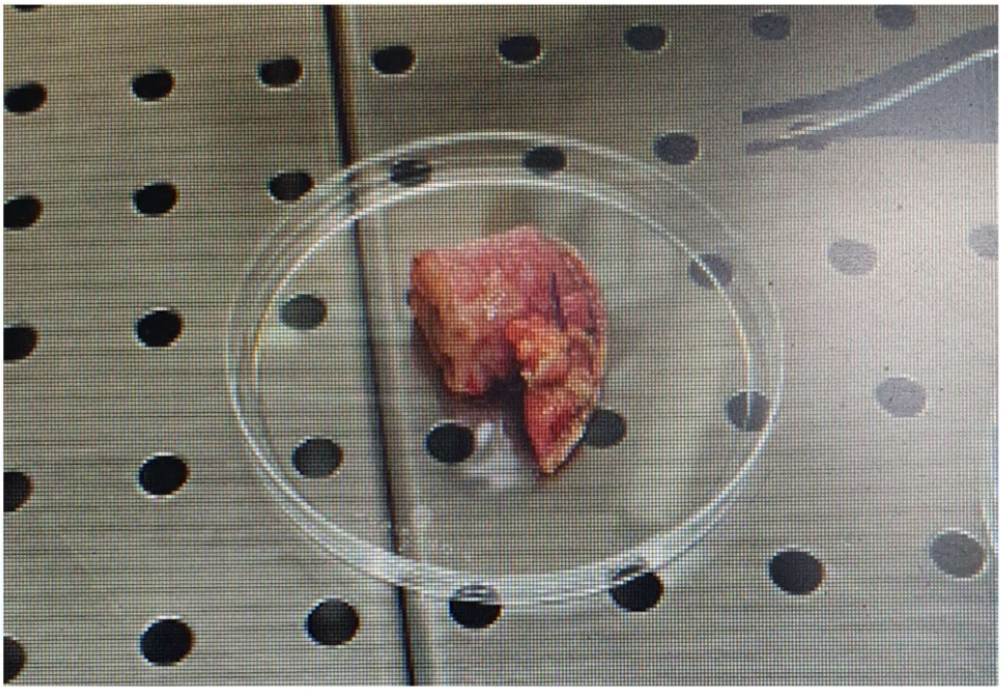

Figure 1. The macroscopic pathological examination revealed a 35 cm intestinal resection, covered by a fibrinous coating, and a fissure of approximately 0.5 cm was found.

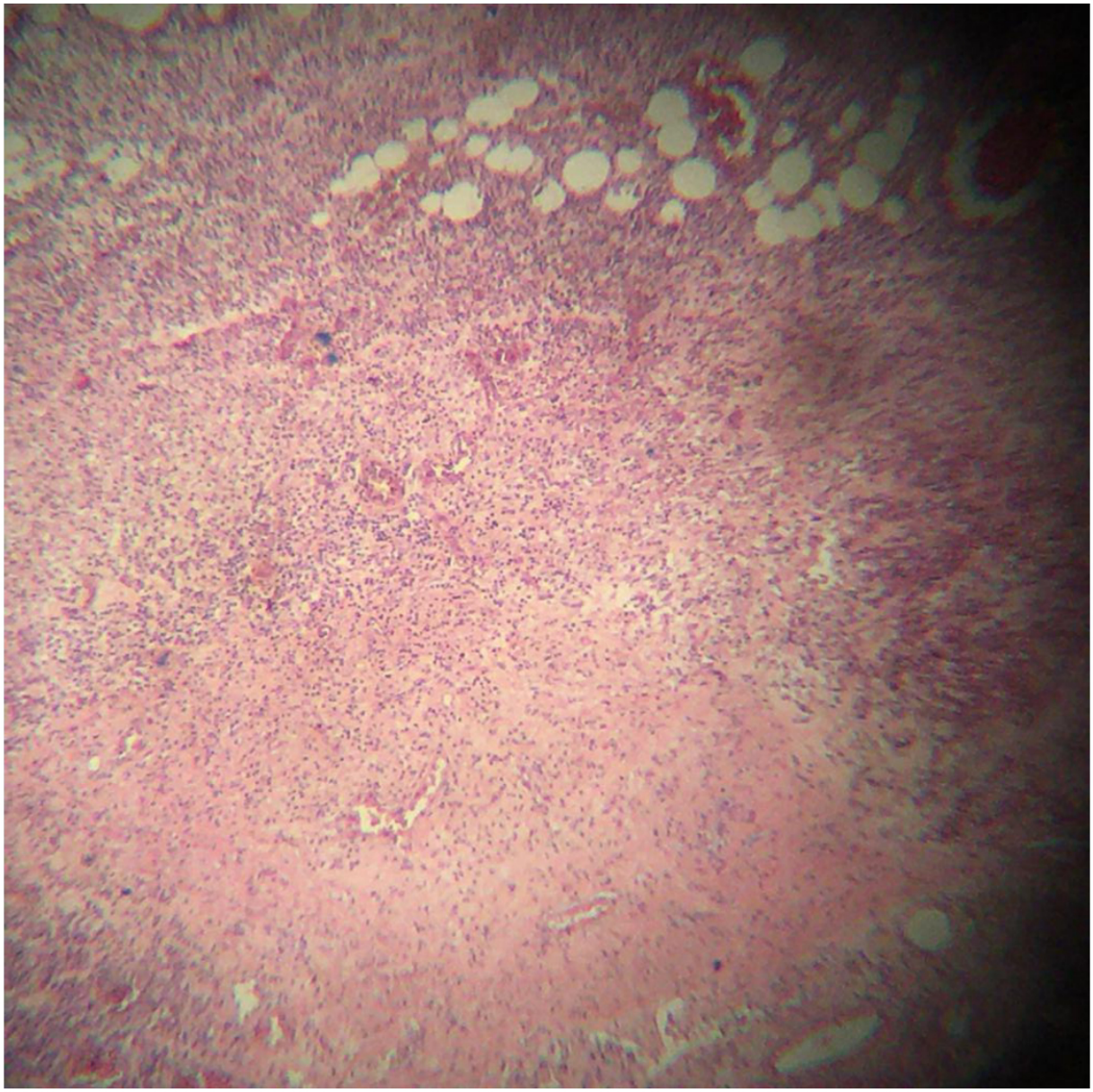

Figure 2. Histological examination of the jejunal sections revealed the presence of widespread acute necrotic-purulent inflammation of the perivisceral serosa.

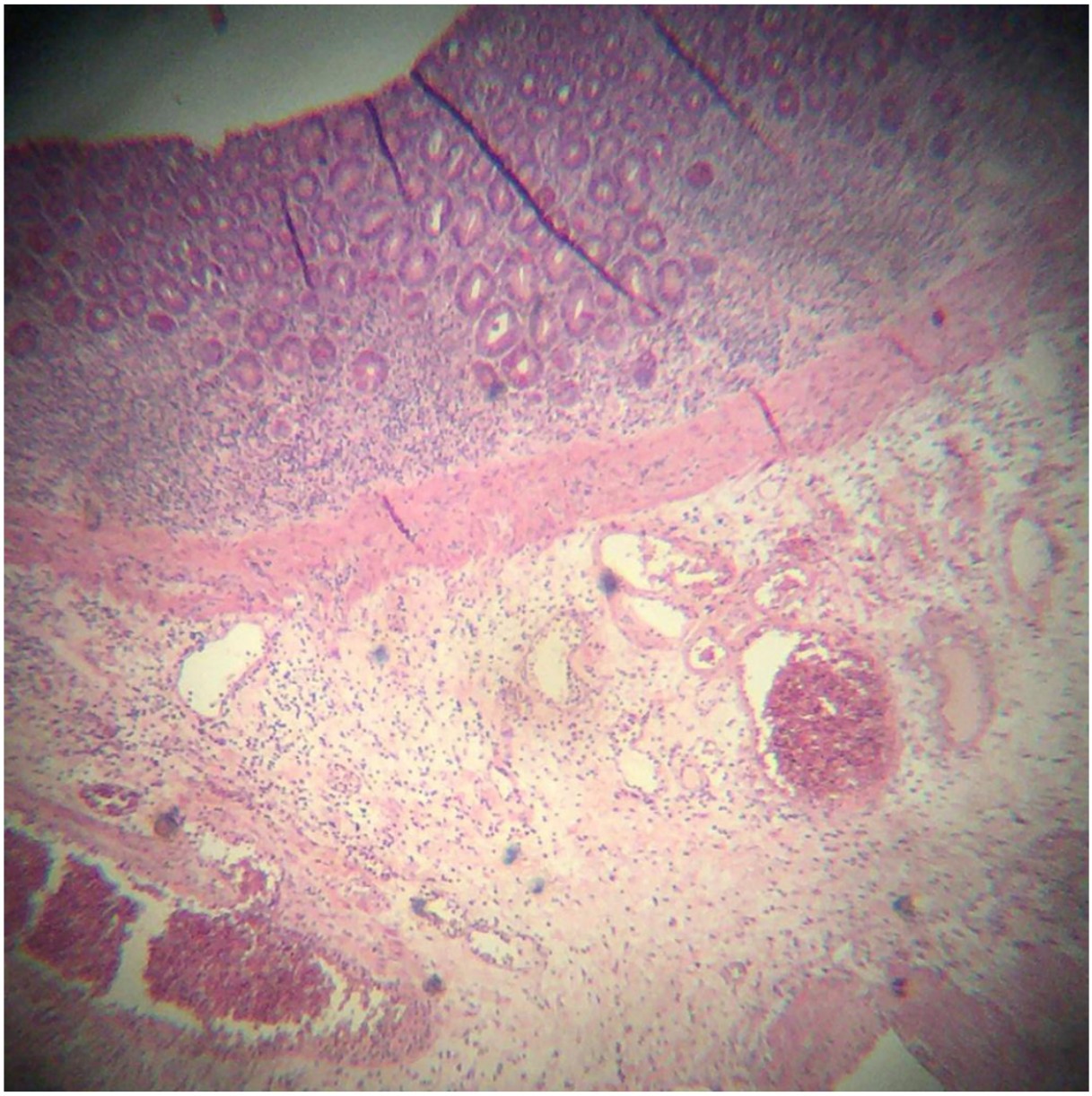

Figure 3. Histological examination of the jejunal sections revealed the presence of widespread acute necrotic-purulent inflammation of the perivisceral serosa.

Contributions: Antonio Mastroianni, conceptualization, writing – original draft preparation, review and editing; Roberto Manfredi, supervision, review and editing; Valeria Vangeli, data curation, formal analysis, methodology; Giuliana Guadagnino, Luciana Chidichimo, Lavinia Berardelli, data curation, formal analysis; Sonia Greco, writing – original draft preparation, review and editing. All authors have read and agreed to the published version of the manuscript.

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Ethics approval and informed consent: this retrospective case-study was approved by the Local Ethics Committee. Written informed consent has been obtained by the patient's family members for the publication of this case report.

Data availability: Data are available on request from the authors.

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